Responsible Use of New Genetic Engineering Techniques

Position paper on the opportunities and risks of applying genome editing in agriculture

New genetic engineering techniques (genome editing) are revolutionising biotechnology

In recent years new techniques have emerged in biotechnology, often known by their technical names or abbreviations such as CRISPR/Cas, TALEN, or zinc-finger nucleases. These techniques, which are often subsumed under the umbrella term "**genome editing**", aim to alter an organism's genetic makeup in specific ways or rewrite parts of it. The term "genome editing" implies that an organism's genetic information can be read as easily as a text and edited at will and with no risk of side effects by modifying a modularly constructed genome. However, this view ignores the complexity of epigenetic effects – i.e. of effects that impact on neighbouring genes or on general gene-regulating mechanisms. The use of these techniques thus involves not only the editing of a text but also **modification of an organism's genome in ways that change its genetic makeup**.

The **CRISPR/Cas method**[1] was only invented in 2012 but it is now used as standard in these new genetic engineering techniques, because by comparison with classical methods of genetic engineering it is simple, quick and cost-effective. Development of the use of the CRISPR/Cas method has advanced rapidly, so that while scientific research continues, market-ready applications – especially in medicine and plant breeding – are already available or will be available soon.

In the main, uses of the CRISPR/Cas method fall into the following categories:

1. **Point mutations**: If the genome is cut by the CRISPR/Cas complex at a point determined by the guide RNA and the DNA strand is subsequently joined by the cell's repair mechanism, there will be small changes in this genome sequence that usually lead to the affected gene being switched off. The changes in the genome are like a point mutation. Using this method, it is also possible to generate a number of small changes or point mutations at different places in the genome simultaneously, so that these combined changes result in the creation of organisms with complex new functions.

2. **Rewriting sections of the genome**: If synthetic DNA segments that differ only very slightly from the original DNA sequence are introduced into the cell at the same time as the CRISPR/Cas complex, these pieces will be used as templates during the repair. The change modelled in the synthetic DNA will then be incorporated into the genome of the target organism.

3. **Introducing additional gene segments**: If additional synthetic DNA containing a sizeable chunk of foreign genetic material as well as the original gene sequence is introduced into the cell with the CRISPR/Cas9 complex, the cell's repair mechanism will copy this and incorporate it.

4. **Gene drive applications**: The CRISPR/Cas method can also be used to propagate an artificially modified gene sequence among the offspring of the modified organism. In

[1] This involves a molecule complex consisting of a DNA-cutting protein (also called a Cas cutting protein or 'genetic scissors') to which a specific guide RNA is attached. The guide RNA takes the CRISPR/Cas complex to a specific place in the genome. Where this RNA binds to the paired (complementary) DNA, the CAS cutting protein severs the DNA.

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, which occur in bacterial DNA. The CRISPR/Cas complex was discovered during research into the immune system of bacteria.

these techniques, which are known as gene drive applications, the classical inheritance rules are overridden in order to transmit one or more modified genes throughout a population. This involves a deliberate and usually irreversible release of the modified organisms.

The CRISPR/Cas method can be used in agriculture to **optimise crops in specific ways**. For example, it is possible to switch off the genome sequences in wheat that make the plant vulnerable to mildew. In the case of wheat, traditional breeding methods based on selecting for resistance properties are extremely time-consuming. Use of the new genetic engineering techniques on a variety of wheat enabled all three genome sequences to be switched off together, thereby making the wheat resistant to mildew. In the USA, “edited varieties” of this sort are already being tested in the field. If these changes enable pesticide use in wheat production to be permanently reduced, this should in principle be welcomed as a contribution to more sustainable agriculture.

The various applications of the CRISPR/Cas method may present risks as well as opportunities. In the view of the Oeko-Institut, these risks cannot be classified clearly in terms of risk potential. In particular, potential unintended effects resulting from release of the modified organisms into natural ecosystems or agricultural environments cannot be ruled out. **The new genetic engineering techniques cannot be regarded as in principle safer than “classical” methods of genetic engineering solely because application is more targeted.**

Unbiased assessment of opportunities and risks is needed

The rapid progress of research into the use of the CRISPR/Cas method for plant breeding opens up the possibility of creating plant varieties resistant to disease faster and with greater precision than has been possible with classical breeding methods. The debate about opportunities and risks should distinguish between different fields of application: the legal, environmental and ethical issues that arise in connection with medical or industrial applications may differ from those that concern agriculture. In view of the development objective of bringing the new genetic engineering techniques to commercial application maturity in agriculture very soon, the Oeko-Institut believes there is an urgent need for analysis and assessment of the resulting opportunities and risks. This should cover both applications in the field of plant and animal breeding and the use of modified microorganisms in the provision of biogenic resources.

It should in particular involve assessing the contribution that the new genetic engineering techniques could make to more sustainable agriculture via developments such as the creation of drought-resistant varieties or the reduction of environmentally damaging agricultural practices (e.g. pesticide use). **A key goal of the accompanying research should be to verify and specify the desired and/or envisaged opportunities of the new genetic engineering techniques in connection with sustainable agriculture.** Evidence of the robustness of the new genetic engineering techniques should be sought. What specific breeding goals are being pursued? How plausible are the current expectations of the application opportunities and the forecasts of their usefulness? What conditions must be present in order to actually realise the benefits in agricultural practice?

At the same time, all intended applications of the new genetic engineering techniques in agriculture must be subjected to a **comprehensive risk assessment** as a matter of course. This applies even to applications of the CRISPR/Cas method that are assumed to be minimally invasive, such as when targeted point mutation is used to switch off genes that are linked to a plant’s vulnerability to a particular disease. The risk assessment should consider not only the effects that the modification is intended to produce but also possible unintended genetic effects or “**off-target effects”**. These could arise if the CRISPR/Cas cutting protein severs the genome at an unintended point in the gene. Current research findings give cause for concern that these off-target effects could be significantly more likely to occur than was previously thought. [2] The epigenetic effects of the CRISPR/Cas method should also be subjected to a risk assessment.

With regard to regulatory risk assessment, the Oeko-Institut considers the following to be essential:

- Evidence-based **review of the desired and/or envisaged precision and accuracy** of the new genetic engineering techniques, e.g. with regard to intervention in the genome and the extent to which unintended genetic and epigenetic effects can be managed.
- It is also important to review the **stability of the functionality thus achieved** (e.g. disease resistance) – i.e. to check whether the effects of using this technique in breeding persist long-term. A special challenge in this context involves evaluating whether the new genetic engineering techniques cause displacement effects with regard to established organic agriculture or even impair it, e.g. through outcrossing.
- Before any release of GMOs into agricultural production, possible **impacts on adjacent ecosystems** must be identified. This applies even to crops modified "only" by CRISPR/Cas point mutation. At present, questions about possible effects on ecosystems remain largely unanswered. Until unforeseen side effects in ecosystems can be reliably excluded, the precautionary principle should be applied and modified plants of this sort should not be approved or released.

In the light of this the Oeko-Institut recommends **nuanced consideration** of the many possible applications of the new genetic engineering techniques. In situations involving irreversible interventions or interventions with potentially high risk to the environment and/or human health, the **precautionary principle** that applies in Germany and the EU requires lawmakers to take steps to minimise risk before possible applications of this technique come onto the market. This means that the precautionary principle must be applied whenever there are scientifically plausible reasons for the existence of a risk (i.e. "initial suspicion" of such a risk). In view of the available evidence that off-target effects may be more frequent than originally supposed, the Oeko-Institut believes that sufficient initial suspicion exists. In this uncertain situation there is therefore a need for **systematic research to accompany the ongoing development of the new genetic engineering techniques. This research should involve systematic and integrated analysis of the opportunities and risks and should actively shape the development process by making concrete recommendations on the best ways of utilising the opportunities and managing the risks.**

Create a reliable legal framework for the new genetic engineering techniques

Against the backdrop of the controversial nature of the issue and the tendency of the general public to be sceptical about classical genetic engineering, the EU's GMO Directive and the German Genetic Engineering Act laid down a regulatory framework tailored to the specific circumstances of classical genetic engineering. In view of the innovative properties of the new genetic engineering methods, the fact that they are readily available to many relatively small businesses (and in some cases even to individuals) and the above-mentioned need for application of the precautionary principle, it is essential to draw up legal guidelines to cover the use of these new methods.

Members of the scientific community disagree on whether and in what situations existing genetic engineering law should be applied to the new genetic engineering techniques. From the

[2] See Kosicki, M., Tomberg, K. & Bradley, A.: Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. Nature Biotechnology, 16 July 2018; online: doi:10.1038/nbt.4192

point of view of the technique-based approach, these methods are covered by genetic engineering law, while from the point of view of a product-based approach they are not.

Some stakeholders suggest that the applicability of genetic engineering law to the new methods should be linked to a threshold (represented by the depth of intervention in the genome). For example, there is discussion of whether there is no need for approval for targeted point mutations (involving modification of fewer than 20 base pairs). If this is the case, it would mean that many CRISPR/Cas applications could be introduced without a risk assessment. However, no scientifically established threshold for the extent of such interventions and the resulting risks is currently in prospect. One must therefore ask whether from a scientific view such a threshold can be justified at all. It is doubtful whether exempting minimally invasive CRISPR/Cas applications from the regulations would ensure reliable protection against the possible risks of the new genetic engineering techniques. Over-hasty exemption of some applications from the risk assessment requirement because they fall below an arbitrarily defined threshold of invasiveness is not consistent with the precautionary principle.

Irrespective of which approach is ultimately adopted, the Oeko-Institut is convinced that regulations should be put in place to create legal certainty with regard to the new genetic engineering techniques**.** This legal certainty is needed by developers and commercial users of the new genetic engineering techniques as well as by end users (such as farmers) and consumers of the products produced by these techniques. People not directly involved are also entitled to have the risk of exposure to possible hazards (e.g. via field trials with gene-drive manipulated insects) minimised by regulation.

The ruling by the European Court of Justice on 25 July 2018 that the new genetic engineering techniques are covered by the GMO Directive has now created a measure of legal certainty for all stakeholders. In its preliminary ruling procedure the ECJ clarified the applicability of the GMO Directive in these cases, especially with regard to scope, intent and purpose and the effects of the mutagenesis exception.

Regulation of the new genetic engineering techniques outside the Genetic Engineering Act – i.e. in accordance with the regulations on crop-growing, food and feed safety and protection of the environment – would not provide the same level of protection as genetic engineering law.

As a result of application of the GMO Directive, the following key principles and instruments of risk assessment and risk management now apply also to the new genetic engineering techniques:

- Approval and monitoring of release trials
- Approval for the marketing of products containing GMOs
- Traceability and retrievability
- Mandatory labelling of food and feed with a GMO content of 0.9 per cent or more
- Freedom of choice for consumers and co-existence with organic agriculture.

However, there are important questions of detail that have yet to be resolved if the above-mentioned regulations are to function in practice. For example, there is a need to define what detection methods and reference materials will apply to each of the new genetic engineering techniques. This is particularly important in relation to the cross-border trade in goods produced by means of the new techniques – for example, imports of corresponding agricultural products from other economic areas such as the USA.

Conclusion

Because they are quick, easy and cheap to use and because of the functions they provide (such as resistance to pathogens in crops), the new genetic engineering techniques open up interesting prospects for more sustainable agriculture. However, in view of the off-target effects that have already been demonstrated, possible epigenetic effects and instances of irreversible applications (such as gene-drive organisms), rigorous application of the precautionary principle is called for. The Oeko-Institut therefore urges that a legal and social framework for further research into and development of the new genetic engineering techniques be created. Such a framework should provide scope for utilisation of the potential opportunities presented by these techniques while also ensuring sufficient protection against possible risks. This has the following concrete implications:

1. **Reliable legal framework for risk assessment and management:** The European Court of Justice's ruling of 25 July 2018 that the GMO Directive also applies to the new genetic engineering techniques means that established rules on risk assessment (e.g. in relation to possible off-target effects and epigenetic effects) and risk management do apply. However, for regulation to be effective, important questions still need to be clarified. For example, the detection methods and reference materials that will apply to each of the new genetic engineering techniques must be specified. The GMO Directive also lacks legally binding definitions of a number of methods that can be used to modify the genetic makeup of a living organism.

2. **Societal discourse:** Appropriate regulation of the new genetic engineering techniques should be based on a societal discourse in order to clarify what social goals are being pursued with these techniques and what "guard rails" should apply to them. This requires a broad dialogue with all affected operators, users and consumers; this dialogue must include representatives of organic agriculture and address the key issues relating to the integrated assessment of opportunities and risks. This includes the question of whether and how the requirements should vary for different applications of the new genetic engineering techniques and, for example, result in an accompanying and graded risk assessment. Case-by-case assessments or court judgements cannot replace the normative questions of the lawmakers that arise in connection with regulation.

3. **Transparent and verifiable information on opportunities and risks:** Acceptance of the crops and foods produced using the new genetic engineering techniques and trust in them, both in agriculture and among consumers, will ultimately depend on how the balance between the specific benefits of a particular application and the possible risks is viewed. The extent to which the information on possible opportunities and risks provided by producers and developers is honest and factual will be an important factor in this. Another important aspect is consumers' freedom of choice on the basis of appropriate labelling and implementation of an effective risk management strategy.

The Oeko-Institut has extensive methodological knowledge and many years' experience of evaluating new technologies and processes and shaping the associated innovation processes. In the light of this we are willing and able to contribute concretely and constructively to planning the priority tasks relating to an informed, development-oriented assessment of opportunities and risks and further development of the legal framework and thus to create the conditions for responsible use of the new genetic engineering methods.

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